



# UNITED STATES PATENT AND TRADEMARK OFFICE

ST

UNITED STATES DEPARTMENT OF COMMERCE  
United States Patent and Trademark Office  
Address: COMMISSIONER FOR PATENTS  
P.O. Box 1450  
Alexandria, Virginia 22313-1450  
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/080,797	02/21/2002	Romulus Kimbro Brazzell	OP/4-31881A	9942

35928 7590 08/08/2005

DLA PIPER RUDNICK GRAY CARY US, LLP  
1625 MASSACHUSETTS AVENUE, NW  
SUITE 300  
WASHINGTON, DC 20036-2247

EXAMINER

ANGELL, JON E

ART UNIT	PAPER NUMBER
----------	--------------

1635

DATE MAILED: 08/08/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

**Office Action Summary**

Application No.

10/080,797

Applicant(s)

BRAZZELL ET AL.

Examiner

Jon Eric Angell

Art Unit

1635

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 23 May 2005.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 1-3,8,27-33,38-41,43 and 45-50 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-3,8,27-33,38-41,43 and 45-50 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

- |  |   |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892)   | 4) <input type="checkbox"/> Interview Summary (PTO-413)<br>Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)                                   | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152)             |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)<br>Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____  |

S-0-2

### **DETAILED ACTION**

This Action is in response to the communication filed on 5/23/2005. Claims 1-3, 8, 27-33, 38-41, 43, 45-50 are currently pending in the application and are addressed herein.

Applicant's arguments are addressed on a per section basis. The text of those sections of Title 35, U.S. Code not included in this Action can be found in a prior Office Action. Any rejections not reiterated in this action have been withdrawn as being obviated by the amendment of the claims and/or applicant's arguments.

#### ***Claim Rejections - 35 USC § 102***

1. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

2. Claims 1-3, 8, 27, 28, 30, 31, 43, and 45-47 are rejected under 35 U.S.C. 102(b) as being anticipated by Leboulch et al. (WO 99/26480, cited as IDS reference AN), for the reasons of record (e.g., see the Action mailed on 3/14/05), reiterated below for convenience.

As previously indicated, Leboulch teaches a method for treating a human patient suffering from diabetic retinopathy (which can result in corneal, retinal and iris neovascularization) by administering to said patient a nucleic acid molecule which expresses endostatin wherein expression of the endostatin polypeptide in the patient inhibits angiogenesis in the vicinity of the retina (e.g., see claim 33, page 33-34). Specifically, Leboulch teaches that the gene therapy vector can be a retroviral vector, adenoviral vector or adenoviral-associated

Art Unit: 1635

vector (AAV) (see p. 5, lines 19-21). Furthermore, Leboulch indicates that the gene therapy vector can be administered by any method that allows the vector to reach the target cells, such as injection to the target tissue, wherein the target tissue can be the retina of the eye (e.g., see p. 11, lines 10-22; and p. 14, lines 2-14; and claim 33). Therefore, Leboulch anticipates the instant claims.

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1 and 29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Leboulch et al. (WO 99/26480, cited as IDS reference AN) in view of Keshet et al. (Journal of Clinical Investigation, 1999) and further in view of Otani et al. (Investigative Ophthalmology & Visual

Art Unit: 1635

Science, 1999) for the reasons of record (e.g., see the Action mailed on 3/14/05), reiterated below for convenience.

As previously indicated, Leboulch teaches a method for treating a human patient suffering from diabetic retinopathy (which can result in corneal, retinal and iris neovascularization) by administering to said patient a nucleic acid molecule which expresses endostatin wherein expression of the endostatin polypeptide in the patient inhibits angiogenesis in the vicinity of the retina (e.g., see claim 33, page 33-34). Specifically, Leboulch teaches that the gene therapy vector can be a retroviral vector, adenoviral vector or adenoviral-associated vector (AAV) (see p. 5, lines 19-21). Furthermore, Leboulch indicates that the gene therapy vector can be administered by any method that allows the vector to reach the target cells, such as injection to the target tissue, wherein the target tissue can be the retina of the eye (e.g., see p. 11, lines 10-22; and p. 14, lines 2-14; and claim 33).

Leboulch does not teach that the method can be used to treat choroidal neovascularization.

Keshet et al. teaches that endostatin is an antiangiogenic peptide that inhibits VEGF activity. Specifically, Keshet et al. teaches, "Endostatin was shown to inhibit VEGF-induced endothelial cell migration in vitro and to have anti-tumor activity in vivo, without any apparent signs of toxicity." (See p. 1500, 1<sup>st</sup> column, lines 3-6).

Furthermore, it was recognized in the art that vascular endothelial growth factor (VEGF) is involved in choroidal neovascularization (CN). For instance, Otani et al. teaches,

"Recent histological and immunohistochemical studies of experimentally produced and surgically excised CNVMs [choroidal neovascular membranes] have indicated that VEGF, transforming growth factor beta (TGF $\beta$ ), acidic fibroblast growth factor (aFGF) and basic fibroblast growth factor (bFGF) are involved in the mechanism of CNVM

Art Unit: 1635

formation associated with ARMD [age-related macular degeneration]. Because VEGF has great selectivity for endothelial cells, it is considered to be a critical angiogenic factor in the development of CNVM, even though the mechanism of CNVM is not fully understood.” (Emphasis added; see paragraph bridging pages 1912-1913).

It is also noted that Otani et al. teaches, “Present findings that Ang2 and VEGF are co-upregulated and that Tie2 is expressed in a variety of cell types in CVNMs further support a crucial role of the interaction between VEGF and Ang2 in pathologic angiogenesis of CNVM formation.” (See p. 1912, Abstract).

Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to use the method taught by Leboulch to ameliorate or reduce the rate of choroidal neovascularization in a subject with a reasonable expectation of success.

Since the teachings of the prior art indicate that (1) Endostatin is an antiangiogenic factor that inhibits VEGF activity, (2) Endostatin can be used in gene therapy methods to inhibit neovascularization, and (3) VEGF is known to be involved in choroidal neovascularization (e.g., see Otani et al.) one of ordinary skill in the art would have been motivated to use the method of Leboulch to inhibit choroidal neovascularization.

Claims 1 and 32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Leboulch et al. (WO 99/26480, cited as IDS reference AN) in view of US Patent 6,106,826 (Brandt et al.) for the reasons of record (e.g., see the Action mailed on 3/14/05), reiterated below for convenience.

As previously indicated, Leboulch teaches a method for treating a human patient suffering from diabetic retinopathy (which can result in corneal, retinal and iris neovascularization) by administering to said patient a nucleic acid molecule which expresses

Art Unit: 1635

endostatin wherein expression of the endostatin polypeptide in the patient inhibits angiogenesis in the vicinity of the retina (e.g., see claim 33, page 33-34). Specifically, Leboulch teaches that the gene therapy vector can be a retroviral vector, adenoviral vector or adenoviral-associated vector (AAV) (see p. 5, lines 19-21). Furthermore, Leboulch indicates that the gene therapy vector can be administered by any method that allows the vector to reach the target cells, such as injection to the target tissue, wherein the target tissue can be the retina of the eye (e.g., see p. 11, lines 10-22; and p. 14, lines 2-14; and claim 33).

Leboulch does not teach that vector is administered intravitreally.

Brandt teaches gene therapy vectors which can be used to deliver therapeutic genes for gene therapy, and specifically teaches an HSV vector as well as an adenoviral vector and adeno-associated vector for use in gene therapy of the eye wherein the vector can be delivered to the eye by intravitreally injecting the vector as well as subretinally and intraocularly delivering the vector, for therapeutic purposes, such as macular degeneration. (e.g., see abstract, column 5, lines 5-20, column 8, lines 57-65, and column 9 lines 15-20).

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time of filing to modify the method taught by Leboulch such that the vector used was delivered intravitreally with a reasonable expectation of success.

The motivation to modify the method of Leboulch is supplied by Brandt who specifically teaches that intravitreal delivery of a therapeutic vector is an effective administration for gene therapy of eye diseases.

Art Unit: 1635

Claims 1, 33 and 38 are rejected under 35 U.S.C. 103(a) as being unpatentable over Leboulch et al. (WO 99/26480, cited as IDS reference AN) in view of US Patent 6,555,107 (Poeschla et al.) for the reasons of record (e.g., see the Action mailed on 3/14/05), reiterated below for convenience.

As previously indicated, Leboulch teaches a method for treating a human patient suffering from diabetic retinopathy (which can result in corneal, retinal and iris neovascularization) by administering to said patient a nucleic acid molecule which expresses endostatin wherein expression of the endostatin polypeptide in the patient inhibits angiogenesis in the vicinity of the retina (e.g., see claim 33, page 33-34). Specifically, Leboulch teaches that the gene therapy vector can be a retroviral vector, adenoviral vector or adenoviral-associated vector (AAV) (see p. 5, lines 19-21). Furthermore, Leboulch indicates that the gene therapy vector can be administered by any method that allows the vector to reach the target cells, such as injection to the target tissue, wherein the target tissue can be the retina of the eye (e.g., see p. 11, lines 10-22; and p. 14, lines 2-14; and claim 33).

Leboulch does not teach that vector is a lentiviral vector or that the vector is a bovine immunodeficiency viral vector.

Poeschla teaches methods of gene therapy for the eye wherein a lentiviral vector, specifically a bovine immunodeficiency vector, is used to deliver and express the therapeutic gene in the eye of the subject. (For example, see abstract, column 2, lines 10-35; column 4, lines 34-41; column 11, 45-55).

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time of filing to modify the teaching of Leboulch such that the gene therapy vector used is the



Art Unit: 1635

bovine immunodeficiency viral vector taught by Poeschla (which is a lentiviral vector) with a reasonable expectation of success.

The motivation to make such a modification is provided by Poeschla. Poeschla teaches that the BIV vector is better for transfecting difficult to target non-dividing cells of the nervous system including eye cells.

Claims 1, 33, 38-41 and 48-50 are rejected under 35 U.S.C. 103(a) as being unpatentable over Leboulch et al. (WO 99/26480, cited as IDS reference AN) in view of US Patent 6,555,107 (Poeschla et al.) and further in view of US Patent 6,106,826 (Brandt et al.) for the reasons of record (e.g., see the Action mailed on 3/14/05), reiterated below for convenience.

As previously indicated, Leboulch teaches a method for treating a human patient suffering from diabetic retinopathy (which can result in corneal, retinal and iris neovascularization) by administering to said patient a nucleic acid molecule which expresses endostatin wherein expression of the endostatin polypeptide in the patient inhibits angiogenesis in the vicinity of the retina (e.g., see claim 33, page 33-34). Specifically, Leboulch teaches that the gene therapy vector can be a retroviral vector, adenoviral vector or adenoviral-associated vector (AAV) (see p. 5, lines 19-21). Furthermore, Leboulch indicates that the gene therapy vector can be administered by any method that allows the vector to reach the target cells, such as injection to the target tissue, wherein the target tissue can be the retina of the eye (e.g., see p. 11, lines 10-22; and p. 14, lines 2-14; and claim 33).

Art Unit: 1635

Leboulch does not teach that vector is a lentiviral vector such as a bovine immunodeficiency viral (BIV) vector or that the lentiviral/BIV vector is administered intraocularly, subretinally or intravitreally.

Poeschla teaches methods of gene therapy for the eye wherein a lentiviral vector, specifically a bovine immunodeficiency vector, is used to deliver and express the therapeutic gene in the eye of the subject. (For example, see abstract, column 2, lines 10-35; column 4, lines 34-41; column 11, 45-55).

Brandt teaches gene therapy vectors which can be used to deliver therapeutic genes for gene therapy, and specifically teaches an HSV vector as well as an adenoviral vector and adeno-associated vector for use in gene therapy of the eye wherein the vector can be delivered to the eye by intravitreally injecting the vector which would necessarily encompass sub-retinal as well as intraocular delivery (e.g., see abstract, column 5, lines 5-20, column 8, lines 57-65, and column 9 lines 15-20).

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time of filing to modify the teaching of Leboulch such that the bovine immunodeficiency viral vector taught by Poeschla (which is a lentiviral vector) is used to deliver and express the therapeutic gene and to deliver the lentiviral/BIV vector by intravitreally, subretinally or intraocularly injecting the gene therapy vector with a reasonable expectation of success.

The motivation to make such a modification is provided in part by Brandt who specifically teaches that adenoviral and AAV vectors can be used to treat eye disease by intravitreally, subretinally or intraocularly delivering the therapeutic vector; and in part by

Art Unit: 1635

Poeschla who teaches that the BIV vector is better for transfecting difficult to target non-dividing cells of the nervous system including eye cells.

### *Response to Arguments*

Applicant's arguments filed 5/23/2005 have been fully considered, but are not persuasive.

With respect to the rejection of claims under 35 USC 102(b) based on the teaching of Leboulch, Applicants argue that case law holds that a genus does not necessarily enable and teach all species encompassed therein (See page 2 of the response). Applicants argue that WO 99/26480 teaches at page 5 a wide range of vectors and at pages 11-14 possibly all conceivable means for administering a biological drug. Applicants assert that an artisan would have a large list of vectors and delivery means from which to choose and to test to obtain the instantly claimed invention. Applicants contend that there is no highlighting and teaching of direct administration of an endostatin expressing vector to the eye as claimed in the instant application. Applicants also argue that WO 99/26480 teaches that transfer of the nucleic acid to appropriate target cells is the critical first step in gene therapy and choice of the particular gene delivery system will depend on such factors as the intended target and the route of administration. Applicants assert that there is no particular teaching of how to deliver the endostatin to the eye using a vector in WO 99/26480. The Applicants also contend that the PCT as a whole, teaches at best, expression of angiostatin with a goal of treating cancer and assert that factors that modulate angiogenesis are distinct and may have different activities in different tissues. Finally, Applicants argue that since WO 99/26480 does not particularly teach making and using

Art Unit: 1635

endostatin for treating non-cancerous disorders and does not particularly teach the eye as the target organ, WO 99/26480 is not enabling for ocular gene therapy and thus does not anticipate the instant claims.

In response, it is respectfully pointed out that claim 33 of WO 99/26480 explicitly claims using gene therapy to treat diabetic retinopathy wherein endostatin expression inhibits angiogenesis in the vicinity of the retina. Furthermore, page 2 (last full paragraph) of the WO 99/26480 document clearly teaches ex vivo and in vivo methods and identifies in vivo therapy as a preferred embodiment. WO 99/26480 also indicates that methods preferably involve delivery of the angiogenesis inhibiting polypeptide using a viral vector or plasmid which can be administered so that cells of the patient in the vicinity of the target site are infected or transfected with the nucleic acid encoding the angiogenic-inhibiting polypeptide. Furthermore, like the instant application, the WO 99/26480 document teaches in detail a number of different viral vectors that can be used to deliver and express the therapeutic endostatin protein (e.g., see page 5). The WO document indicates that the term “a gene therapy vector” is meant to mean a vector useful for gene therapy and can be a virus, plasmid or phage (see page 5). The WO 99/26480 document teaches, “preferred vectors include, e.g., retroviral vectors, adenoviral vectors, adeno-associated vectors, herpes virus vectors, Similiki Forest Virus-based vectors, Human Immunodeficiency Virus, Simian Immunodeficiency virus, and non-viral plasmids” (see page 5). Additionally, page 9 of the WO 99/26480 document teaches, in detail, a preferred embodiment in constructing a gene therapy vector that is sufficient for use in the treatment of angiogenesis in vivo. WO 99/26480 also explicitly teaches that the eye is a specific target for the delivery of the therapeutic nucleic acid (e.g., see page 14, lines 1-15). Therefore, WO 99/26480 teaches each

Art Unit: 1635

and every element of the instant claims. It is acknowledged that a disclosure of a broad genus does not anticipate an undisclosed species; however, the WO 99/26480 document teaches the particular species encompassed by the claims. Furthermore, in view of claim 33 of the WO 99/26480 document, the selection of the claimed species are not taken out of context of the teachings of the WO 99/26480 document. The WO 99/26480 document clearly teaches using a vector that expresses endostatin for inhibiting angiogenesis in the eye of a patient suffering from diabetic retinopathy, and discloses a number of specific vectors and methods of administration for accomplishing the treatment.

Therefore, considering all of the above as a whole, WO 99/26480 clearly teaches using a nucleic acid vector such as an adenoviral vector to express endostatin for treating a human patient suffering from diabetic retinopathy wherein the nucleic acid vector is delivered to the eye of the patient such that nucleic acid vector expresses endostatin polypeptide in the eye thereby inhibiting angiogenesis in the eye.

With respect to Applicants arguments that the WO 99/26480 document does not provide an enabling disclosure for the claimed method, it is noted that case law states that anticipation does not require the actual creation or reduction to practice of the prior art subject matter; anticipation requires only an enabling disclosure. (*In re Donohue*, 766 F.2d 531, 533 [226 USPQ 619] (Fed. Cir. 1985)). A reference may enable one of skill in the art to make and use a compound even if the author or inventor did not actually make or reduce to practice that subject matter. (*Bristol-Myers*, 246 F.3d at 1379; see also *In re Donohue*, 766 F.2d at 533).

In the instant case, the WO 99/26480 document provides sufficient guidance to reasonably enable a direct application of an endostatin expressing vector to mitigate or reduce

Art Unit: 1635

angiogenesis in the eye of a patient suffering from a disease associated with an abnormally high level of angiogenesis. It is noted that the level of predictability parallels what is taught in the prior art regarding gene therapy of the eye as well as gene therapy for treating a tumor and/or angiogenesis in a patient in need of treatment by direct administration of a gene therapy construct. For instance, US Patent 6,638,502 (previously cited) teaches direct administration of a gene therapy vector expressing an anti-angiogenic factor for treatment of tumors (e.g., see the working Examples). Also, see US Patent 5,827,702 (previously cited), which teaches using a recombinant adenoviral vector for delivery of a gene of interest to different parts of the eye. For instance, the '702 patent teaches directly delivering the vector to choroid ocular cells in a mouse wherein a gene of interest encoded by the vector is expressed in the choroids ocular cells (e.g., see Example 3). Also see the previously cited prior art including US Patent 6,201,104, US Patent 6,106,826, US Patent 6,555,107 (all previously cited) which also indicate the state of the prior art of gene therapy of the eye. Additionally, the instant specification also acknowledges numerous techniques for increasing gene expression in the eye by direct administration (e.g., see p. 8, p. 9--especially the third full paragraph, p. 10, p. 11 and p. 13).

Furthermore, the Applicants have not indicated any specific critical element that the WO 99/26480 document fails to teach which prevents the document from providing an enabling disclosure. It is acknowledged that the WO 99/26480 document does not disclose a working example for the indicated method. However, in view of the state of the prior art with respect to gene therapy of the eye as well as the state of the art with respect to using endostatin as an anti-angiogenic factor in gene therapy, the WO 99/26480 document does provide a sufficient disclosure to enable the indicated method.

The Applicants also refer to an article submitted as an exhibit wherein LeBoulch is quoted as saying “We could not see an effect of endostatin anyway we tried”, and indicate that this is evidence that the WO 99/26480 document is not enabled. In response, it is noted that the article also indicates LeBoulch as acknowledging that the negative results in mice do not prove Folkman is wrong about endostatin—thus indicating that the negative results do not prove that endostatin does not work. Furthermore, as indicated above, the disclosure of the WO 99/26480 document in view of the state of the prior art is sufficient to enable the method of inhibiting angiogenesis in the eye of a patient using a vector that expresses endostatin.

With respect to the rejection of claims under 35 USC 103, Applicants argue that since all of the rejections are based on the teachings of LeBoulch (WO 99/26480), and since the WO 99/26480 document does not anticipate or enable the base claims for the reasons indicated above, then the rejections are improper (e.g., see pages 4-6 of the response filed 5/23/2005). Furthermore with respect to the rejection of claims as being obvious over WO 99/26480 in view of Keshet et al. and further in view of Otani et al., Applicants argue that the secondary references do not cure the deficiencies of WO 99/26480.

In response, the Examiner disagrees that the WO 99/26480 document does not anticipate or enable the claimed method, for the reasons indicated above.

Furthermore, with respect to Applicants arguments regarding the rejection based on WO 99/26480 in view of Keshet et al. and further in view of Otani et al., the Applicants appear to be arguing against the references individually. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413,

Art Unit: 1635

208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Therefore, Applicants arguments are not persuasive and the rejection of is not withdrawn.

### ***Conclusion***

No claim is allowed.

**THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jon Eric Angell whose telephone number is 571-272-0756. The examiner can normally be reached on Mon-Fri, with every other Friday off.



Art Unit: 1635

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader can be reached on 571-272-0760. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Jon Eric Angell, Ph.D.  
Art Unit 1635

*Anne Marie Falk*  
**ANNE-MARIE FALK, PH.D.**  
**PRIMARY EXAMINER**